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(54) Title: ANTIBACTERIAL DENTAL MATERIALS

(57) Abstract

The present invention concerns a group of dental restorative and luting cements that have been combined with antibacterial compounds and thereby have achieved an increased antibacterial activity against oral microorganisms. The cements can be based on glasspolyalkenoats or dental composite resins, to be applied in thicker layers compared to a varnish, thereby containing a larger amount of antibacterial compounds. The antibacterial compound(s) are leaking from the cement(s) which have been made soluble in oral fluids, having the properties of a matrix that allow sustained release of a drug.

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ANTIBACTERIAL DENTAL MATERIALS

The present invention concerns a group of dental restorative and luting cements which have been combined with antibacterial compounds and thereby have achieved an increased antibacterial activity against oral microorganisms. The cements can be based on glasspolyalkenoats or dental composite resins, to be applied in thicker layers compared to a varnish, thereby containing a larger amount of anitbacterial compounds. The antibacterial compound(s) are leaking from the cement(s) which have been made soluble in oral fluids, having the properties of a matrix that allow sustained release of a drug.

Dental caries and periodontitis are caused by microbial plaques on the tooth surfaces. Bacteria belonging to the Streptococus mutans group are strongly associated with the developement of caries. These microorganisms are highly sensitive to chlorhexidine in various forms as chlorhexidine-gluconate, chlorhexidine-acetate and chlorhexidine-hydrochloride.

Patients with extensive dental decay often carry mutans streptococci in high numbers, and a causal treatment can be to treat the patient with chlorhexidine gluconate gel, which is applied on the teeth in costumefit trays. By this treatment, the mutans streptococci are eliminated from the mouth for a period of time but very seldom for ever. To maintain a situation with no or occasional mutans streptococci, the treatment has to be repeated after a few months. One reason for reappearence is probably that some microorganisms persists in retentive areas where the concentration of the chlorhexidine is not bactericidal. Another reason is that the concentration of chlorhexidine in this type of treatment is high and other microorganisms will also be more or less eliminated. In an environment where several species have been more or less eliminated and then start at the same time to struggle for survival and recolonization, the mutans streptococci will soon find its ecological nisch again.

Therefore, it is apparent that if chlorhexidine could be administered in such a way that an initially high concentration is present on the teeth to eliminate all mutans streptococci and that the concentration gradually decreases allowing other microorganisms that are less sensitive to the drug to colonize first, the highly sensitive mutans streptococcus would have less chance to survive. This has been demonstrated in part by Sandham and co-workers (1). Sandhams group used a varnish containing chlorhexidin, Sumatra benzoin and ethanol

However, the varnish was *per definition* very thin and the procedure had to be repeated at least three times, in different sessions, to be somewhat successful.

The present invention is a thicker layer of resin or cement as carrier, which can contain substantially more chlorhexidine or other antibacterial compunds compared to a convetional varnish.

The idea to mix antibacterial compounds such as chlorhexidine with dental restorative materials is not new. Jedrychowski and co-workers have described a combination of chlorhexidine with composite resin or glass polyalkenoate cements (2). By mixing the antibacterial compund with the restorative materials, they achieved antibacterial effects without comprising the mechanical properties of such materials.

The present invention describes a dental cement that is in contrast to the above, highly soluble in oral fluids and will dissolve after 1-4 weeks on the teeth. This important feature of the material will give a delivery system were a high concentration of an antibacterial compound is combined with a dissolving carrier. It is not an advantage to either have a non-soluble carrier (2) or lower concentration (1) of antibacterial compounds if one is aiming at eliminating mutans streptococci from the teeth, as in a profylactic approach towards the treatment of dental caries. If a restorative material is permanently placed in a cavity, the damage in terms of a cavity has already been done. If a non-soluble material is placed on sound dental surfaces, eventually, it will lose its antibacterial properties and become a retention site for microorganisms and increase the risk of disease.

The present invention can be described by the following example. Glasspolyalkenoate materials such as a restorative cement (Chemfil, De Trey Dentsply Ltd, England) or a luting cement AquaCem (De Trey Dentsply) are mixed with water containing various amounts of chlorhexidine gluconate or acetate rangeing from 0 to 20 per cent. Discs are made and placed on agar medium containing an inoculum of mutans streptococci or lactobacilli. After incubation, an inhibition zone is seen around the discs corresponding to the amount of chlorhexidine present in the disc. The same discs are transferred to freshly inoculated agar plates repeatedlty, until their antibacterial properties are lost. The results show that the cements has a small antibacterial effect even without addition of chlorhexidine, perhaps due to the high fluoride content

The addition of chlorhexidine gives a clear dose-response inhibition of the bacterial growth. The antibacterial effect is maintained through at least 15 changes of freshly inoculated bacteria with 48 hours of incubation each time. A corresponding antibacterial effect is seen when bacteria are grown in a broth medium and incubated with the chlorhexidine containing discs. The high fluoride content is also important as a caries preventive measure.

When exceding 10 per cent of chlorhexidine in added water to the cements, a substantially higher solubility of the cements is seen. As an example, the addition of 15 per cent chlorhexidine gluconate to the luting cement will render it totally dissolved after 8-10 changes in agar plates as described above. This is an example how the glasspolyalkenoates can become soluble by the addition of high concentrations of chlorhexidine. This addition does not dramatically affect the adhesive properties of the materials and they will attach to dental surfaces even containing high amounts of chlorhexidine. If a lower concentration of chlorhexidine is used the material could be used as a temporary filling material.

The chlorhexidine is relased from the discs as determined by spectrophotometric measurements at 251nm.

The glasspolyalkenoates has the advantage of containing a substantial amount of fluoride which is also released from the material, making the tooth structures less susceptible to decay.

The above presented formulations of glasspolyalkenoates and chlorhexidine are commonly used in dentistry and they have a low toxicity. Of course, the concept of the invention can be applied not only on glasspolyalkenoates and chlorhexidine, but also dental resin materials and other materials combined with other antibacterial compounds.

Literature cited:

1. Sandham, HJ et al. 1988. A preliminary report on long-term elimination of detectable mutans streptococci in man. Journal of Dental Research 67(1):9-14

2. Jedrychowski JR et al. 1983. Antibacterial and mechanical properties of restorative materials combined with chlorhexidines. Journal of oral rehabilitation 10: 373-381.

Claims:

1. A dental cement-, resin- or restorative material containing an antibacterial compound as for example chlorhexidine, which is slowly released from said material.

2. A dental cement-, resin- or restorative material adhering to tooth surfaces and containing an antibacterial compound as for example chlorhexidine, which is slowly released from said material.

3. A glasspolyalkenoate material according to claims 1 and 2 containing 10 - 40 per cent chlorhexidine (gluconate, acetate or hydrochloride) which is slowly released.

4. A glasspolyalkenoate material according to claim 3, that has been made soluble in oral fluids by the addition of chlorhexdine

5. A glasspolyalkenoate material containing chlorhexidine up to 15 per cent or other antibacteraial compound where the glasspolyalkenoate has been made soluble by the addition of other compounds.

6. A dental cement-, resin- or restorative material containing an antibacterial compound as for example chlorhexidine, which is slowly released from said material that has the properties of beeing soluble in oral fluids

7. A dental cement-, resin- or restorative material containing an antibacterial compound as for example chlorhexidine, which is slowly released from said material that has the properties of beeing completely soluble in oral fluids in 5 to 25 days.

8. A dental cement-, resin- or restorative material adhering to tooth structures containing an antibacterial compound as for example chlorhexidine, which is slowly released from said material that has the properties of beeing completely soluble in oral fluids in 5 to 25 days.

9. A material according to claims 1 - 8 containing fluoride.

10. A material according to claims 1 - 9 that can be applied on a tooth surface in a substantially thicker layer as compared to a conventional varnish.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00253

**I. CLASSIFICATION OF SUBJECT MATTER** (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A61K 6/02

**II. FIELDS SEARCHED**

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| IPC 4 | A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

**III. DOCUMENTS CONSIDERED TO BE RELEVANT** [9]

| Category * | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| X | EP, A2, 0 128 655 (UNIVERSITY OF TORONTO INNOVATIONS FOUNDATION) 19 December 1984 & US, 4496322 JP, 60004123 | 1 - 10 |
| X | EP, A2, 0 140 766 (THE FORSYTH DENTAL INFIRMARY FOR CHILDREN) 8 May 1985 & JP, 60099245 AU, 570506 US, 4764377 | 1 - 10 |
| X | EP, A2, 0 223 245 (MITSUI PETROCHEMICAL INDUSTRIES, LTD.) 27 May 1987 & JP, 62201806 JP, 63115829 | 1 - 10 |
| X | EP, A2, 0 243 002 (ROHTO PHARMACEUTICAL CO) 28 October 1987 & JP, 62223115 | 1 - 10 |

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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**IV. CERTIFICATION**

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 1989-08-23 | 1989 -08- 30 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| Swedish Patent Office | Jack Hedlund |

**FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**

| | | |
|---|---|---|
| X | EP, A2, 0 264 660 (IVOCLAR AG) 27 April 1988 & DE 3634697 | 1 - 10 |
| X | Chemical Abstracts, Vol. 99 (1983), abstract No. 99:181435h, J. Oral Rehabil. 1983, 10(5), 373-81 (Eng). | 1 - 10 |

**V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]**

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

**VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]**

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.